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GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***1058/Del/2002*** *dated* ***22nd October 2002.***

Witness my hand this 23rd day of December2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

1052/DEL/2002

22 OCT 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 , Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF STABLE PHARMACEUTICAL COMPOSITIONS OF GANCICLOVIR"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. RAJEEV SHANKER MATHUR
b. PANANCHUKUNNATH MANOJ KUMAR
c. SUNILENDU BHUSHAN ROY
d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501 - 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, RAJEEV SHANKER MATHUR, PANANCHUKUNNATH MANOJ KUMAR, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(RAJEEV SHANKER MATHUR)

b.

(PANANCHUKUNNATH MANOJ KUMAR)

c.

(SUNILENDU BHUSHAN ROY)

d.

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Statement and Undertaking on FORM – 3
c. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 684470 dated 13/09/2002 on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **23RD** day of **September, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

1052

FORM 2

22 OCT 2002

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR THE PREPARATION OF STABLE PHARMACEUTICAL COMPOSITIONS OF GANCICLOVIR

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to stable pharmaceutical compositions of 9-(1,3-dihydroxy-2-propoxymethyl) guanine commonly known as ganciclovir containing more than 1% water content.

Ganciclovir is a well-known anti-viral agent. It is an acyclic nucleoside analogue of 2'-deoxy guanosine that inhibits replication of herpes virus. Ganciclovir has been shown to be active against cytomegalovirus (CMV) and herpes simplex virus (HSV) in human clinical studies.

US Patent No. 4,199, 574 discloses ganciclovir generically. Ganciclovir and its salts having anti-viral activity were first disclosed in US Patent No. 4,355,032 by Syntex Inc. This patent describes the p reparation of ganciclovir and also outlines the manufacture of pharmaceutical dosage forms containing the same.

In a subsequent Patent US 4,642,346, Syntex Inc. disclosed a novel extremely stable anhydrous crystalline form of ganciclovir containing less than 1% water of hydration. The earlier disclosed form has been reported to be unstable owing to its hygroscopic nature and causes handling and formulating problems. The anhydrous form has been shown to be unusually resistant to water absorption and has better physical characteristics than the known hydrate form. Because of its non-hygroscopic nature, it retains better physical appearance over a longer period of time, thus enhancing the appearance of the dosage form and increasing consumer acceptance.

We have surprisingly found that it is possible to prepare a stable formulation with ganciclovir containing more than 1% of water content.

Ganciclovir is a high dose drug and therefore drug characteristics play an important role in determining the characteristics of the final formulation. We have found that even when the active used in the formulation is ganciclovir having more than 1% water content instead of anhydrous crystalline ganciclovir disclosed in the prior art, it does not absorb substantial amount of moisture or cause handling or formulating problems. Furthermore, the formulation containing ganciclovir, which has water content of more than 1% exhibited acceptable stability.

In fact, without intending to be limited by theories, we feel that the water content helped in binding of the drug and excipients thereby helping in formulating.

It is an object of the present invention to provide a stable and robust pharmaceutical formulation comprising ganciclovir having more than 1% water content.

It is another embodiment of the present invention to provide a stable pharmaceutical composition comprising ganciclovir containing more than 1.5% water content.

The invention thus comprises of preparing a solid unit dosage form comprising ganciclovir having 1% or more water content, by granulating ganciclovir or a pharmaceutically acceptable salt thereof, according to the methods known in the art; followed by compression of the granules into a tablet or filling them into a hard gelatin capsule.

Ganciclovir may be granulated with the excipients using any of the conventional methods used in the art including wet granulation, dry granulation or direct compression. In the "wet" granulation method, the dry solids (active ingredients, filler, disintegrant etc.) are blended and moistened with the binder solution and agglomerates or granules are build up of the moistened solids. Wet massing is continued until a desired homogeneous particle size has been achieved whereupon the granulated product is dried. Dried granules are blended with lubricants and optionally, a disintegrant and the blend is compressed into a tablet or filled into hard gelatin capsules.

Another method for manufacture of granulates is the "dry" granulation method in which the active can be compacted alone or together with other pharmaceutically acceptable excipients. The granules are then mixed with extragranular excipients and compressed into a tablet or filled in hard gelatin capsules.

Thus, in one embodiment of the invention, the present invention relates to a tablet dosage form prepared by compression of granules of active and pharmaceutically acceptable excipients obtained by "wet" granulation method or "dry" granulation method.

In another embodiment, the present invention relates to a capsule prepared by filling granules of active and pharmaceutically acceptable excipients obtained by "wet" granulation method or "dry" granulation method in a hard gelatin capsule.

The density of the granules as measured by the "bulk density" and "tapped density" is an important parameter for this formulation. The difference between these two densities describes the cohesiveness and compressibility of the substance. These two parameters are particularly important for capsule dosage form and decide the optimum filling of the capsule. Bulk density of atleast 0.6 g/ml and tapped density of less than 0.8 g/ml is preferred to achieve the optimum filling of the capsules.

Pharmaceutical compositions in accordance with the present invention comprises ganciclovir in a desired amount admixed with one or more pharmaceutically acceptable excipients selected from the group consisting of diluents, disintegrants, binding agents, wetting agents, lubricants and anti-adherent agents.

The solid unit dosage form according to the invention may contain a filler selected from lactose, starch, mannitol, sorbitol, dextrose monohydrate, microcrystalline cellulose, dibasic calcium phosphate dihydrate, sucrose-based diluents, monobasic calcium sulphate monohydrate, calcium sulphate dihydrate, calcium lactate trihydrate, powdered cellulose and the like.

The binding agent used in accordance with the present invention is selected from those commonly known in the art. Such binding agents impart sufficient cohesion to the powders to permit normal processing such as sizing, lubrication compression and packaging, but still permit the composition to disintegrate and dissolve upon ingestion. Examples of binding agents include acacia, tragacanth, sucrose, gelatin, glucose, starch, alginic acid, polyethylene glycol, guar gum, polysaccharides, bentonites, polyvinylpyrrolidone, cellulose ethers such as hydroxypropyl methylcellulose and hydroxypropyl cellulose. The binding agent is preferably present from about 0.05% to about 5% w/w of the formulation.

The disintegrants used in accordance with the present invention include, either individually or in combination starches, sodium starch glycolate, clays, celluloses

such as purified cellulose, methylcellulose and sodium carboxymethylcellulose, alginates, pre-gelatinized corn starches, crospovidone, gums. Disintegrants can be added at any suitable step during the preparation of the pharmaceutical composition, particularly prior to granulation or during the lubrication step prior to compression or filling the dosage form. In the present invention, disintegrant is present both intragranularly as well as extragranularly.

Croscarmellose sodium is the preferred disintegrant and may be present from about 0.5 to about 7% w/w of the formulation. We have observed that use of disintegrant intragranularly as well as extragranularly enhances the disintegration time appreciably. The extragranular disintegrant is present from about 0.5% - 3% w/w of the formulation, preferably they are present at 1.5 - 2.5% w/w of the formulation.

The pharmaceutical compositions of the present invention optionally comprises one or more lubricants and /or glidants. Suitable lubricants and/or glidants include glyceryl behenate, metallic stearate such as magnesium stearate, stearic acid, hydrogenated vegetable oils, talc, waxes, boric acid, sodium benzoate, polyethylene glycols and sodium stearyl fumarate. The lubricant used in the present formulation is present in an amount of about 0.1% to about 2.0% w/w preferably about 0.1% to about 1.5%. Use of magnesium stearate as lubricant is preferred.

Unit formula for ganciclovir dosage form is given but is not intended to limit the scope of the invention.

UNIT FORMULA OF GANCICLOVIR DOSAGE FORM

Ingredients	Amount (mg)
Intragranular	
Ganciclovir	500
Microcrystalline cellulose	0.45
Polyvinyl pyrrolidone	16.2
Croscarmellose sodium	11.0
Extragranular	
Magnesium stearate	1.35
Croscarmellose sodium	11.0
Total weight	540

The process for preparing ganciclovir dosage form are exemplified herein but should not be considered to limit the scope of the invention.

Example 1

Ganciclovir is sifted with croscarmellose sodium and microcrystalline cellulose and granulated with a solution of polyvinyl pyrrolidone in water. The granules are dried and blended with magnesium stearate and croscarmellose sodium (extragranular). The blend is filled into a hard gelatin capsule or is compressed into a tablet.

Example 2

Ganciclovir is sifted with croscarmellose sodium, polyvinyl pyrrolidone and microcrystalline cellulose. This blend is compacted and then broken to generate granules. The granules are mixed with magnesium stearate and croscarmellose sodium (extragranular). The blend is filled into a hard gelatin capsule or is compressed into a tablet.

Different formulations containing variable percentages of water were subjected to stability and moisture uptake studies as shown in Table 1 and Table 2.

Ganciclovir containing 1% or more water content was subjected to moisture uptake at 25°C and 60% RH in open petridish and the increase of weight was monitored. The data presented in Table 1 demonstrates there is no appreciable increase in moisture during storage.

TABLE -1

Moisture uptake by ganciclovir

Time (hrs)	Moisture gain (% w/w)
2.0	0.12
4.0	0.38
8.0	0.46
48.0	0.49
168.0 (1 week)	0.50

Accelerated stability testing was conducted by varying the water content of ganciclovir. The packages of final product were stored at 40°C and 75% RH for a period of 3 months. At predetermined intervals, some of the packages are opened and analyzed to determine the amount of active ingredient, water content and related impurities (RS) present in the formulation. Data generated shows that the formulation does not pick up substantial amount of water and is quite stable during the storage period.

TABLE – 2

Water content of ganciclovir (% w/w)	Storage (Months)	Assay (%)	Total RS (%) (Except Guanine)	Water Content
1.99	0	97.90	0.837	5.19
	1	95.96	0.849	5.02
	2	94.48	0.841	5.02
	3	94.24	0.818	5.17
2.54	0	102.0	0.315	4.48
	1	100.7	0.335	5.12
	2	100.4	0.426	4.98
	3	99.8	0.318	4.96

WE CLAIM:

1. A process for the preparation of a stable and robust pharmaceutical composition comprising ganciclovir having more than 1% water content.

2. The process according to claim 1 wherein the water content is more than 1.5%.

3. The process according to claim 1 or 2 wherein the process comprises granulation of ganciclovir alone or with other pharmaceutically acceptable excipients.

4. The process according to claim 3 wherein the granulation is carried out by wet granulation.

5. The process according to claim 3 wherein the granulation is carried out by dry granulation.

6. The process according to claim 3 wherein other pharmaceutically acceptable excipients selected from the group consisting of diluents, disintegrants, binding agents, wetting agents, lubricants and anti-adherent agents.

7. The process according to claim 6 wherein the filler is selected from lactose, starch, mannitol, sorbitol, dextrose monohydrate, microcrystalline cellulose, dibasic calcium phosphate dihydrate, sucrose-based diluents, monobasic calcium sulphate monohydrate, calcium sulphate dihydrate, calcium lactate trihydrate, powdered cellulose and the like.

8. The process according to claim 6 wherein said binding agent includes acacia, tragacanth, sucrose, gelatin, glucose, starch, alginic acid, polyethylene glycol, guar gum, polysaccharides, bentonites, polyvinylpyrrolidone, cellulose ethers such as hydroxypropyl methylcellulose and hydroxypropyl cellulose.

9. The process according to claim 8 wherein the binder is present in a concentration of 0.05% to 5% w/w of the formulation.

10. The process according to claim 6 wherein the disintegrant includes starches, sodium starch glycolate, clays, celluloses such as purified cellulose, methylcellulose and sodium carboxymethylcellulose, alginates, pre-gelatinized corn starches, crospovidone, gums and mixtures thereof.

11. The process according to claim 10 wherein the disintegrant is present in a concentration of about 0.5% to about 7% w/w of the formulation.

12. The process according to claim 10 wherein a portion of the disintegrant is present extragranularly.

13. The process according to claim 12 wherein the extragranular disintegrant is present at concentration of about 0.5% to about 3% w/w of the formulation.

14. The process according to claim 3 wherein the granules produced after granulation process is filled into a capsule.

15. The process according to claim 3 wherein the granules produced after granulation process is compressed into a tablet.

16. The process according to claim 3 wherein the granules produced after granulation process has bulk density of at least 0.6 g/ml.

17. The process according to claim 3 wherein the granules produced after granulation process has tapped density of less than 0.8 g/ml.

18. A process for the preparation of a stable and robust pharmaceutical composition comprising granulating ganciclovir having more than 1% water content and one or more pharmaceutically acceptable excipients with binder solution followed by drying the granules, mixing with extragranular excipients, compressing the resultant blend into a tablet or filling into a capsule.

19. A process for the preparation of a stable and robust pharmaceutical composition by dry compaction of ganciclovir having more than 1% water content with one or more pharmaceutically acceptable excipients, breaking the compacts to generate granules followed by mixing with extragranular excipients, compressing the resultant blend into a tablet or filling into a capsule.

20. A process as described and exemplified herein.

Dated this 23RD day of SEPTEMBER, 2002.

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to a process for the preparation of a stable and robust pharmaceutical composition of ganciclovir containing more than 1% water content. The water content of ganciclovir may vary from about 1 to 10%.